METHOD FOR MANUFACTURING MICROFLUIDIC CHIP WITH ELECTROOSMOTIC FLOW CONTROLLED BY INDUCING ELECTRIC FIELD THROUGH SELF-ASSEMBLED MONOLAYER

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a method for manufacturing a microfluidic chip with electroosmotic flow (EOF) controlled by inducing an electric field through a self-assembled monolayer, particularly to a method including a step of forming an insulating layer on a bottom plate of the microfluidic chip so as to induce a perpendicular electric field, wherein the insulating layer is a self-assembled monolayer (SAM). The microfluidic chip can be easily obtained with an extremely thin insulating layer, and the voltage for inducing is very low. Additionally, size of the chip is effectively reduced, and electroosmotic flow (EOF) thereof can be controlled as required in its flowing direction and velocity.

EOF has advantages of being easily induced, having a flat flowing profile, and needing no extraordinarily large pump system. Therefore, EOF can be utilized in a lab-on-a-chip system or a microfluidic control system by means of a micro-electromechanical system (MEMS). One of the most prevailing and matured MEMS

applications is a capillary electrophoresis microchip matched with various detecting systems in the field aforementioned. Recently, capillary electrophoresis microchips utilizing the characteristics of the electroosmotic flow (EOF) have been successfully used for separation and detection of DNA, protein, environmental or biochemical substances, and microbes.

The invention offers an innovative and simple method for manufacturing a microfluidic chip or a capillary electrophoresis microchip which has a microfluidic effectively controlled and consumes little energy. Furthermore, without changing strength of the longitudinal driving electric field externally added, velocity and direction of the electroosmotic flow (EOF) can be controlled timely.

2. Description of Prior Art

Currently, flowing direction and velocity of micro fluid in a bio-microchip systems are controlled by pneumatics, hydrodynamics or electrokinectics. Particularly, the electrokinectics can move hydrated cations or anions in an electric double layer on the surface of a micro channel to drive the fluid to flow by an electric field. When the hydrated cations (anions) absorbed near by the channel wall move toward an (cathode) anode within the electric field, liquid in the micro channel also flows, i.e., electroosmotic flow (EOF) is produced. However, when the fused-silica tube is larger than 3, the surface of the capillary wall

represents strong negative electricity. Therefore, the EOF can move only along the direction of the electric field, but not in the inverse direction.

FIG. 8 shows a traditional capillary tube. At pH larger than 3, the silanol groups on the inner surface 4 decompose into silicon-oxygen anions and presents electrically negative. The hydration cations in the solution will be attracted to the inner surface of the capillary tube to form an electric double layer. By supplying an external voltage to the capillary tube, EOF may be induced and facilitates separation of samples.

In general, EOF is easily influenced by pH values of the buffer liquid, ionic strength of the electrolyte solution and functional groups of the inner surface of the capillary tube, and therefore flowing velocity and direction of the solution in the capillary channel are difficult to be controlled.

In 1990, Lee et al. disclosed a method, in which a capillary tube is supplied with a radial external voltage to induce polarization of inner wall through the wall 4 (shown in Fig. 8) and change zeta potential ζ (the potential of the electric double layer), and thus the flowing direction and velocity of EOF are controlled. Additionally, conductive solution, ionized gas and conductive polymers are also provided for controlling the zeta potential (ζ). However, such devices still exist the following disadvantages:

1. Thickness of walls of common capillary tubes may range from tens to hundreds micrometer, which needs thousands volts of the radial external voltage to produce an electrically inducing field for polarization.

2. Surface of the capillary tube presents negative when the pH value is larger than 3, and therefore negative electroosmotic flow (EOF) (contrary to direction of the electrical field) cannot be produced to meet the requirement of controlling flowing direction; and

3. Capillary tubes are difficult to form a network of an electroosmotic flow (EOF), so that functions including transportation, switching, mixing and separating of samples can not be achieved.

All the abovementioned methods relates to design of capillary tubes. In order to control EOF in a micro-channel, Schasfoort et al. disclosed a method utilizing a semiconductor manufacturing way. As shown in Fig. 9, an insulating layer 5 of silicon nitride (390 nm thick) is formed on a silicon base for inducing an electric field. A micro channel 6 is constructed in the silicon base by means of lithography technique. The base is then combined with a glass bottom member by means of anodic bonding. Then an electric field is induced to directly control the surface potential of the micro channel 6, and subsequently the flowing direction of the EOF may be controlled. The flowing velocity can be controlled with an external inducing gate voltage (+50V ~ -50V). The maximum flowing velocity of the EOF can attain $\mu_{eof}=3.4cm^2V^{-1}s^{-1}\times10^4$

(environmental liquid at pH 3.6). However, when the pH value of the environmental liquid is larger than 3.6, for example, pH 4.5, the polarization of channel surface caused by the external inducing voltage cannot overcome the natively negative charge produced on the inner wall surface of the micro channel 6, and only one-way positive electroosmotic flow (EOF) can be induced. Additionally, in a chip made by bonding glasses, glass serves as the insulating layer 5 (50 μm thick) to control the EOF. In a chip made of PDMS and a silicon base, silicon dioxide can serve as the insulating layer 5 (5μm thick). However, these devices exist the following disadvantages:

1. The thickness of the insulating layer 5 and the material of the micro channel 6 necessitate voltage as high as tens to hundreds volts, and the flowing direction and velocity of the EOF cannot be arbitrarily controlled when the pH value is larger than 3. The traditional environmental liquid for biological experiments is about pH 7.0 so that the EOF can only be controlled in the same direction as the electric field;

2. The insulating layer 5 cannot be formed unless a complicated microfabrication process is used; and

3. The insulating layer 5 is generally as thick as hundreds nanometers to several micrometers. At the same induced electric field, the larger insulator thickness is, the smaller the surface potential is induced.

Therefore, it is necessary to develop an improved method for manufacturing microfluidic chip to solve the problems of the traditional methods.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a method for manufacturing a microfluidic chip with electroosmotic flow (EOF) controlled by inducing an electric field through a self-assembled monolayer (SAM) so that direction and velocity of the EOF can be controlled.

The method of the present invention is primarily to combine a top plate and a bottom plate; wherein the bottom plate has a gate electrode on an upper surface thereof and has the SAM formed on said gate electrode. The top plate has an elongate micro channel groove which is narrower than that of the gate electrode, recessed in a lower portion thereof and filled with a buffer solution. Accordingly, the flowing direction and the flowing velocity of said EOF are controlled by supplying high voltage to two ends of said micro channel groove to provide an electric field for driving EOF and supplying an inducing voltage to the gate electrode for controlling the polarization of SAM surface. The SAM of the present invention can be easily formed and thin enough to lower inducing voltage required for controlling the

surface potential of SAM and have a smaller chip size. Furthermore, direction and velocity of the EOF can be controlled regardless of the acidic or neutral solution filled in the channel.

BRIEF DESCRIPTION OF DRAWINGS

This invention will be better understood by referring to the accompanying drawings, wherein:

FIG. 1 is an exploded perspective view of the microfluidic chip made according to the present invention;

FIG. 2 is a cross section of the microfluidic chip made according to the present invention;

FIG. 3 is a cross section of an end surface of the microfluidic chip made according to the present invention;

FIG. 4 is a perspective view of a mold for manufacturing a top plate in the present invention;

FIG. 5 is a diagram of electroosmotic flow (EOF) produced in the micro channel in the present invention;

FIG. 6 shows the relation between mobility of the EOF and induced voltage obtained in the present invention, with ODT being SAM;

FIG. 7 shows the relation between mobility of the EOF and

induced voltage obtained in the present invention, with MUDA being SAM;

FIG. 8 shows the condition of an electroosmotic flow (EOF) produced in a conventional micro channel; and,

FIG. 9 shows the condition of an electroosmotic flow (EOF) produced in another conventional micro channel.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

FIG. 1 shows the microfluidic chip made according to the present invention, which primarily includes a bottom plate 1 and a top plate 2 combined together.

The bottom plate 1 includes a rectangular substrate 11, an elongate and extremely thin gate electrode 12 provided on an intermediate portion, an insulating layer 13 formed on an upper surface of the gate electrode 12. The top plate 2 is also rectangular and adapted to be combined with the bottom plate 1. An elongate micro channel 21 narrower than the gate electrode 12 is formed in a recess of a lower portion of the top plate 2. Two cylinder-like storage reservoirs 22 filled with buffer solution are respectively formed at two ends of the micro channel 21 and communicate with the micro channel 21.

In using the microfluidic chip, high voltage power is supplied to the two ends of the micro channel 21 so as to produce an electric field

for driving EOF, and an inducing voltage Vg is supplied to the gate electrode 12 to induce a perpendicular electric field for controlling the surface potential of the insulation layer 13 under the micro channel 21. Accordingly, potential of an electric double layer can be controlled, and flowing direction and velocity of the EOF can be further controlled.

To produce the SAM of the invention, a solution of a chemical agent is first prepared, and then the substrate 11 with the gate electrode 12 is immersed in the chemical agent solution for a certain period of time, for example, 18-24 hours. During immersing, the chemical agent contained in the solution may interacts with the surface of the gate electrode 12 to form a SAM film as the insulating layer 13. The insulating layer 13 formed on the bottom plate 1 is a single-molecular layer and extremely thin, which significantly distinguishes the present invention from the conventional procedures.

Four methods for forming the SAM on the gate electrode are as follows:

1. Combination of an alkanoic acid ($C_nH_{2n+1}COOH$) and metal cations (such as aluminum oxide and silver) on the surface of the gate electrode;

2. Combination of an organosilicon derivative (such as alkylchlorosilane, alkylaminosilane, and alkyalkoxysilane) and hydroxyl groups on the surface of the gate electrode;

3. Adsorption of organic sulfur (such as n-alkyl sulfide,

thiophenol, and thiophene) to the gate electrode coated with transition metal on the surface thereof, for example, alkanoic thiol adsorbed to the surface of the gate electrode 12 made of gold or silver; and

4. Adsorption of alkyl groups to the surface of the gate electrode made of silicon.

In the present invention, the top plate 2 is preferably made of flexible and soft material such as poly(dimethylsiloxane) (PDMS). Therefore, the top plate 2 can be attached to the bottom plate 1 through van der Waals' force by slightly pressing the both.

Detailed procedures of a preferred embodiment for manufacturing the microfluidic chip is described below.

First, organic sulfur (1-octadecanethiol; ODT, (Aldrich)) is dissolved in 2 mM of pure alcohol (99.5 %). A glass substrate 11 with the gold gate electrode 12 is then immersed in the solution. To form the gold gate electrode 12, chromium is previously deposited on the glass substrate 11 and then gold is deposited thereon. The gold/chromium electrode is 100/30 nm thick, 1.2cm long and 100μm wide.

At the same time, a source electrode 14 and a drain electrode 15 are respectively formed at two end portions of the glass substrate 11 to function as input terminals of high voltage. Further, a conductive wire 16 is provided on the substrate 11 for connecting with the gate electrode 12 to function as an input terminal of voltage for inducing an electric field. Next, the substrate 11 is immersed in the solution for 18-24 hours

to form the insulating layer 13 of SAM on the gate electrode 12, and the bottom plate 1 is completed.

FIG. 4 shows a mold 3 for manufacturing the top plate 2 in the present invention. The mold 3 has an elongate rectangular bar 31 of 13μm height, 50μm width and 1.5cm length formed on the intermediate portion of a silicon substrate by means of standard lithography. Then a mixture of poly dimethylsiloxane (PDMS) monomer and a curing agent in the proportion of 10 : 1 is poured into the mold 3 and heated for 1 hour at 90 ℃ for hardening. After the PDMS curing, the mold 3 is removed to leave the top plate 2 with the micro channel 21. Two storage cylinders 22 are bored at two ends of the micro channel 21, as shown in FIG. 1.

In the present invention, the top plate 2 made of PDMS is elastic and soft, and the bottom plate 1 made of glass is completely flat. Therefore, the top plate 2 and the bottom plate 1 can be attached to each other through van der Waals' force by slightly pressing with a finger.

In using the microfluidic chip, as shown in FIGs. 1, 2 and 5, high voltage is supplied to the source electrode 14 and the drain electrode 15 to produce an electric field for driving electroosmotic flow (EOF), and an inducing voltage is supplied to the conductive wire 16 to induce an perpendicularly electric field; so that the inducing voltage may control surface potential of the insulating layer 13 of SAM. The inducing voltage ranges from +0.8V to -0.8V. When the voltage of the

gate electrode 12 is positive, the induced positive surface potential may attract anions of the buffer solution existing in the micro channel 21 to form an electric double layer. Under high voltage power, the electroosmotic flow (EOF) has an inverse direction to the electric field, and is called the negative EOF, as shown in FIG. 5. On the contrary, when the inducing voltage of the gate electrode 12 is negative, the electroosmotic flow (EOF) has the same direction as the electric field, thus called the positive electroosmotic flow (EOF). Additionally, flowing velocity of the electroosmotic flow (EOF) can be adjusted by properly controlling the inducing voltage.

Examples and Test Mode

In order to verify effects of the microfluidic chip of the invention in controlling the direction and the velocity of the EOF, tests are performed by using two organic sulfuric compounds, ODT and MUDA. ODT (octadecanethiol) has a methyl group ($-CH_3$) and MUDA has a carboxyl group (-COOH). The insulating layer 13 of SAM is formed on the gold gate electrode 12 of the glass substrate 11. Then the bottom plate 1 and the top plate 2 made of PDMS are combined together to obtain two different microfluidic chips for tests.

For each chip, high voltage power is supplied to the two ends of the micro channel 21 to produce an electric field of 80 V/cm and drive EOF, and inducing gate voltage (Vg) ranging from +0.8V to -0.8V

is supplied to the gate electrode 12. Thus, the micro channel 21 filled with buffer solution of pH 6.0 or 3.0 receives inducing voltages of different volts and polarities. The relation between the electroosmotic fluid (mobility) (μ_{eof}) and the inducing gate voltage (Vg) of the gate electrode were observed and measured, as shown in FIGs. 6 and 7.

Since both ODT and the surface of the PDMS micro channel 21 include methyl groups, direction and strength of the EOF mobility (μ_{eof}) can be completely controlled by controlling strength and polarity of the gate voltage; regardless of pH values of the buffer.

For the insulating layer 13 made of MUDA, the carboxyl groups on the surface will decompose into negative charges at pH 6.0. Therefore, if the gate voltage is negative, the negative surface potential of the insulating layer 13 is strengthened, and the EOF mobility is larger than that of ODT. Even though the gate voltage is positive, the positive potential induced still cannot overcome the natively negative surface potential, and the total surface potential is negative. As a result, the EOF mobility cannot perform inverse control, and the total surface potential is smaller than that of ODT. However, the carboxyl groups on the surface won't decompose at pH 3.0, and therefore direction and magnitude of the EOF mobility (μ_{eof}) can be controlled.

Table 1 shows the inducing efficiencies of the conventional microfluidic chips aforementioned and those obtained in the present invention. Compared with the conventional microfluidic chips

developed by the lithography since 1999, the insulating layer made of SAM obviously exhibits the best effect in controlling the EOF mobility (μ_{eof}). The magnitude and direction of the EOF can be linearly controlled with magnitude and polarity of the inducing voltage (Vg); even though the buffer solution is at pH 6.0. The required inducing voltage Vg of the invention is the least, but the control factor is one hundred times as large as the others. Test results verify that the microfluidic chip made according to the present invention can effectively and completely control the flowing direction and velocity of the electroosmotic flow (EOF) with voltage even less than 1.0V.

Table 1

	pH Value of the Buffer Solution	Insulating Layer		Inducing Voltage, Vg (V)	Electroosmotic Flow (EOF) Mobility ,μ_{eof} ($x10^4cm^2/V.s$)	Control Factor, $\Delta\mu_{eof}/\Delta Vg$ ($x10^4cm^2/V^2.s$)
		Material (nm)	Thickness (nm)			
Reference 1	3.6	Si_3N_4	390	25~37	-2.0~1.5	5.6
Reference 1	4.5	Si_3N_4	390	50~50	4.3~6.0	1.7
Reference 2	3.0	SiO_2	50000	172~52	-1.1~1.9	4.0
Reference 3	3.0	SiO_2	2000	460~300	-0.9~2.9	0.5
Reference 3	5.0	SiO_2	2000	460~300	1.2~3.4	0.3
the Present Invention	3.0	ODT	2.9	0.8~0.8	-3.1~3.3	400.0
the Present Invention	6.0	ODT	2.9	0.8~0.8	-3.1~3.4	406.3

Reference:

1. R. B. M. Schasfoort, S. Schlautmann, J. Hendrikse, A. van den Berg. Science 286, 942 (1999).

2. N. A. Polson, M. A. Hayes, Anal, Chem. 72, 1088 (2000).

3. J. S. Bush, P, -C. Wang, D. L. Devoe, C. S. Lee, Electrophoresis 22, 3902 (2001).

According to the above description, the invention shows advantages as follows:

1. The insulating layer (SAM) can be easily manufactured and modified only by immersing in a proper solution for chemical adsorption or covalent bonding; and hydrophobicity/hydrophilicity and surface potential of the modified layer can be varied with different functional groups;

2. The insulating layer (SAM) can be made extremely thin, within several nanometers so that the inducing voltage may be less than 1.0 V and induced with a dry battery, which minimizes both cost and system size;

3. The zeta potential (ζ) controlled by the surface potential can control the flowing direction and the flowing velocity of the electroosmotic flow (EOF) as desired, regardless of acidic or neutral solution, and therefore the chip is suitable for serving as a liquid pump to drive liquid flow through the micro channel;

4. The zeta potential (ζ) controlled by the surface potential can control and increase the concentration of the micro particles in the tested solution in the micro channel. In other words, low accuracy resulting from insufficient samples of pathogen test and protein can be greatly

promoted by controlling the gate electrode. That is, the chip of the invention can enlarge signal by increasing concentration;

5. The insulating layer (SAM) needs only very low voltage, and therefore biochips made by the same are suitable for implanting in a patient's tissue with medicine therein. In addition, dosage of the medicine can be controlled according to feedback signal varied with secretions of the tissue so as to reduce side effects, since the SAM and low zeta potential are harmless to human body;

6. As the SAM induced with the low gate voltage (less than 1.0V) is quite stable in a solution of pH 3.0 regardless of pH value of body fluid, and therefore suitable for being implanted in a human body for a long period of time without being destroyed or affected by body fluid.

While the preferred embodiments of the invention have been described above, it will be recognized and understood that various modifications may be made therein and the appended claims are intended to cover all the modifications that may fall within the spirit and scope of the invention.